Statements Under 37 C.F.R. § 1.825(a) and (b)

Applicants herewith submit a paper copy of a Substitute Sequence Listing (6 pages) and, a computer-readable diskette containing the Substitute Sequence Listing. The Substitute Sequence Listing (paper copy and computer readable form (CRF)) is submitted herewith to comply with current format requirements under 37 C.F.R. § 1.823 and § 1.824.

As such, in accordance with 37 C.F.R. § 1.825(a), the undersigned attorney for Applicants hereby states that sequence information contained in the Substitute Sequence Listing submitted herewith is identical to the sequence information contained in the Substitute Sequence Listing submitted with original Application No. 08/464,600. The Substitute Sequence listing is completely supported by the specification as originally filed, and no new matter has been introduced.

In accordance with 37 C.F.R. § 1.825(b), the undersigned attorney for Applicants hereby states that the information in the paper copy of the Substitute Sequence Listing submitted herewith is identical to the information contained in the computer readable form of the Substitute Sequence Listing submitted herewith.

Remarks

The specification has been amended to add priority information and headings, to bring the references to Figures 1A-B in the specification into conformity with the formal drawings of Figures 1A-B submitted herewith, to add the American Type Culture Collection ("ATCC") accession number of the specified deposited plasmid, as well as the address for the ATCC, to correct minor typographical errors, and to bring the Sequence Listing into compliance. No new matter has been added by way of amendment to the specification.

Conclusion

Entry and consideration of the above amendments and remarks are respectfully requested.

Respectfully submitted,

Date: November 15, 2001

Jonathan L. Klein Reg. No. 41,119
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (301) 251-6015

JLK/DS/ba

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kunsch et al.

Atty. Docket No.: PF198D1C1

Application Number: Unassigned

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Examiner: Unassigned

Title: Human Hepatoma-Derived Growth Factor-2

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 4, the second full paragraph has been amended as follows:

Figures 1A-B depict the cDNA sequence (SEQ ID NO:1) and corresponding deduced amino acid sequence (SEQ ID NO:2) of HDGF-2. The standard one letter abbreviation for amino acids is used. Sequencing was performed using a 373 Automated DNA sequencer (Applied Biosystems, Inc.).

At page 4, the fourth full paragraph has been amended as follows:

In accordance with an aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the mature polypeptide having the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the cDNA of the clone deposited [as ATCC Deposit No. on _____] with the American Type Culture Collection (ATCC, located at 10801 University Boulevard, Manassas, Virginia 20110-2209) as ATCC Deposit No. 97163 on May 24, 1995.

At page 4, the sixth paragraph, extending onto page 5, has been amended as follows:

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature

polypeptide may be identical to the coding sequence shown in [Figure 1] Figures 1A-B (SEQ ID NO:1) or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature polypeptide as the DNA of [Figure 1] Figures 1A-B (SEQ ID NO:1) or the deposited cDNA.

At page 5, the first paragraph has been amended as follows:

The polynucleotide which encodes for the mature polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the deposited cDNA may include, but is not limited to: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.

At page 5, the third full paragraph has been amended as follows:

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

At page 5, the fourth full paragraph has been amended as follows:

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in [Figure 1] Figures 1A-B (SEQ ID NO:2) or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of [Figure 1] Figures 1A-B or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

At page 6, the first full paragraph has been amended as follows:

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in [Figure 1] Figures 1A-B (SEQ ID NO:1) or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

At page 7, the last paragraph, extending onto page 8, has been amended as follows:

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 90%, and more preferably at least 95% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which either retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNAs of [Figure 1] Figures 1A-B (SEQ ID NO:1) or the deposited cDNA(s).

At page 9, the first full paragraph has been amended as follows:

The present invention further relates to an HDGF-2 polypeptide which has the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

At page 9, the second full paragraph has been amended as follows:

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such

polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

At page 9, the fourth full paragraph has been amended as follows:

The fragment, derivative or analog of the polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide and employed for purification of the mature polypeptide. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

At page 32, the second full paragraph has been amended as follows:

The DNA sequence encoding HDGF-2, ATCC [# ___] No. 97163, is initially amplified using PCR oligonucleotide primers corresponding to the 5' sequences of the protein and the vector sequences 3' to the gene. Additional nucleotides corresponding to the gene are added to the 5' and 3' sequences respectively. The HDGF-2 5' oligonucleotide primer has the sequence 5' ACGT**GGATCC**GCGGCTGTGAGTCTGCGGCTCGGC 3' (SEQ ID NO:3) contains a BamHI restriction enzyme site. The 3' sequence 5' CAAC**AAGCTT**TCACCTAGGAAGAAGGAGGTCTTCA 3' (SEQ ID NO:4) contains complementary sequences to a HindIII site and is followed by TGFa-HII coding sequence.

At page 33, the first full paragraph has been amended as follows:

The DNA sequence encoding the full length HDGF-2 protein, ATCC [#___] No. 97163, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene:

At page 34, the second full paragraph, extending onto page 35, has been amended as follows

The vector pA2 (modification of pVL941 vector, discussed below) is used for the expression of the HDGF-2 protein using the baculovirus expression system (for review see: Summers, M.D. and Smith, G.E. 1987, A manual of methods for baculovirus vectors and insect cell culture procedures, Texas Agricultural Experimental Station Bulletin NO:1555). This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by the recognition sites for the restriction [endonucleases .] endonucleases. The polyadenylation site of the simian virus (SV)40 is used for efficient polyadenylation. For an easy selection of recombinant viruses the beta-galactosidase gene from E.coli is inserted in the same orientation as the polyhedrin promoter followed by the polyadenylation signal of the polyhedrin gene. The polyhedrin sequences are flanked at both sides by viral sequences for the cell-mediated homologous recombination of cotransfected wild-type viral DNA. Many other baculovirus vectors could be used in place of pA2 such as pRG1, pAc373, pVL941 and pAcIM1 (Luckow, V.A. and Summers, M.D., Virology, 170:31-39).

At page 35, the first full paragraph has been amended as follows

The plasmid is digested with the restriction [enzymes and] enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The DNA is then isolated from a 1% agarose gel using the commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.). This vector DNA is designated V2.

At page 37, the first full paragraph has been amended as follows:

The plasmid construction strategy is described as [follow] follows:

At page 37, the second full paragraph has been amended as follows

The DNA sequence [encoidng] encoding HDGF-2, ATCC [# ____] No. 97163, contained in the plasmid vector pBluescript was amplified by PCR with a pBluescript vector primer (T3) at the 5' end and a HDGF-2 specific primer at the 3' [endo] end of the HDGF-2 coding sequence containing an XhoI restriction site. After amplification via PCR, the resultant PCR product is digested with BamHI and XhoI and ligated into a modified pcDNA-

1 vector containing the HA tag in frame following the XhoI [restricition] restriction site. The resultant plasmid contains the 5' untranslated region of HDGF-2 followed by the entire coding sequence fused in frame to the HA tag at the C-terminus.